

Peer review file

Article information: <http://dx.doi.org/10.21037/jtd-20-3352>

Reviewer A

Comment 1:

The comorbidities and previous medical conditions vary by races and regions. They should describe these basic characteristics of the study population. In addition, their status of pectus excavatum (type, severity, etc.) should also be provided.

Reply 1:

We thank the reviewer for addressing this central issue. The vast majority of patients were of Danish ancestry, while very few patients were from neighboring countries (Sweden, Germany) – we estimate that $\geq 95\%$ of our population were of Northern European ethnicity. Unfortunately, we could not obtain exact data about the patients' pectus excavatum status or ethnicity as this information was not systematically specified in the medical charts. Furthermore, as the patients were operated between 2001 to 2012, we could not obtain preoperative chest x-rays in order to quantify the pectus excavatum severity with the Haller index. In general, as specified in the manuscript (l. 110-112), the operation indication at our center was moderate to severe pectus excavatum based on clinical evaluation. This has been further clarified in the methods section.

Changes in the text:

Ll. 110-112: "Between 2001 to 2012, 1,046 patients diagnosed with moderate to severe pectus excavatum based on clinical examination underwent surgical correction with the modified Nuss procedure ad modum Pilegaard (10)."

Comment 2:

They included congenital disease and acquired or sporadic diseases without separation. I think thhigat incidental or sporadic disease should be excluded. If they want to include, they should provide the assumption of the association between them.

Reply 2:

We discussed the issue of categorization of comorbidities and previous medical conditions intensely within the author group prior to formal data analysis. We chose to categorize according to the affected organ system as we believe that this gives the most simple but also the most comprehensive presentation of our data. In addition to this, we highlighted the most relevant conditions separately. As mentioned in the

Background section, the aim of this present study was an exploratory investigation into the pectus excavatum phenotype by assessing *all* conditions associated with the pectus deformity in our large cohort. In contrast to previous studies, we did not wish to limit our exploration to specific disease entities, as some of these are already inquired into. We believe that the scientific value and originality of this study lies in this disposition.

Changes in the text:

None.

Comment 3:

Although a large-scale clinical study was performed, I think that this study's findings are nothing new and not interesting. They should provide more selective and interesting study about, such as the association between severity and comorbidity. I recommend that they had better focus on the highly prevalent or relevant diseases.

Reply 3:

We appreciate the opinion of the reviewer. However, we believe that this study adds several important points to the understanding of the pectus excavatum phenotype including 1) dispute of the findings in other studies with regard to high prevalences of cardiac conditions and connective tissue syndromes, 2) our pectus excavatum cohort seems to be comparable to the background populations regarding comorbidity profile, which concurs with the notion that this patient category can be considered healthy, as stated by reviewer A.

Regarding our disposition of placing emphasis on all comorbidities and previous conditions, we kindly refer to the reply addressed to comment 2.

Changes in the text:

None.

Reviewer B

Comment 4:

As the authors have mentioned in discussion, there are no data on the background population or control group that can be compared, so it seems to be difficult to express their conclusions. Therefore, it would be better to analyze and compare the data of the control group.

Reply 4:

We thank the reviewer for addressing this central issue. As the reviewer points out, we have clearly emphasized this issue in the manuscript. The reasons for the lack of a control group lies in the danish medical chart systems which is divided into three areas; 1) hospital medical records, 2) primary care medical records (unavailable to researchers), and 3) large diagnosis-based registers. Our data was based on assessment of hospital medical charts which complicates the sampling of a control group. Sampling a control group based on hospital medical charts would in this case cause significant information bias, as information only exists from previously hospitalized patients and only from the time of hospitalization. Thus, as most the common conditions as asthma, allergies etc. are managed in primary care, these would be severely underestimated in the control group, thereby causing major risk of a type I error.

To further clarify the issue of this study's lacking control group, we have elaborated on this in the manuscript.

Changes in the text:

Ll. 114-116: "Hospital medical records were retrospectively assessed between 2018 to 2019 and information was registered on gender, date of birth, date of operation, past medical history requiring hospitalization or known comorbidities registered at the time of surgery."

Ll. 215-227: "No control group could be sampled based on hospital medical records for comparison, as information would only be accessible for hospitalized patients at the time of hospitalization. This would underestimate prevalances of comorbidities in the control group and imply major risk of bias. Therefore, it is not possible to thoroughly discern differences in the comorbidity burden in pectus excavatum patients compared to the background population."

Comment 5:

(line 21-22) It seems that this this patient category are comparable to the background population in this regard.

---> It seems that this patient category is comparable to the background population in this regard.

Reply 5:

We thank the reviewer for pointing out this error.

Changes in the text:

Ll. 59-61: "It seems that this patient category is comparable to the background population in this regard and our findings do not support screening this patient category for associated conditions."

Comment 6:

(line 52) the modified Nuss procedure ad modum Pilegaard at xx Hospital.

---> the modified Nuss procedure ad modum Pilegaard. (reference)

Reply 6:

We agree with the reviewer and have changed this sentence.

Changes in the text:

Ll. 110-112: "Between 2001 to 2012, 1,046 patients diagnosed with moderate to severe pectus excavatum based on clinical examination underwent surgical correction with the modified Nuss procedure ad modum Pilegaard (10)."

Comment 7:

(line 167-220) References

Sources should be referenced according to the Vancouver reference style. In text references should be identified using numbers in round brackets.

The titles of journals should be abbreviated according to the style used in Index Medicus.

For reports with up to three authors, all the author names should be listed. However, if a report has more than three authors, the first three authors should be listed followed by "et al."

- McLeer-Florin A, Lantuéjoul S. Why technical aspects rather than biology explain cellular heterogeneity in ALK-positive nonsmall cell lung cancer. *J Thorac Dis* 2012;4:240-1.

- Lin X, Li W, Lai J, et al. Five-year update on the mouse model of orthotopic lung transplantation: Scientific uses, tricks of the trade, and tips for success. *J Thorac Dis* 2012;4:247-58.

Reply 7:

We have edited the reference list according to the recommendations by the reviewer.

Changes in the text:

Ll. 259-301, the set-up of the references has been change accordingly.

Comment 8:

Table 1: Baseline characteristics of the study population including number of comorbidities per patient

---> Table 1: Baseline characteristics of the study population

Reply 8:

This has been changed according to the reviewer's recommendation.

Changes in the text:

L. 303: "Table 1: Baseline characteristics of the study population"

Comment 9:

(Table 1 and 2) All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in this order)

Reply:

We thank the reviewer for pointing out this omission. This issue has been addressed in the table texts for table 1 and 2.

Changes in the text:

Ll. 303-308: Table 1 and 2.

Reviewer C

Comment 10:

My major concern with this study is that it only focusses on general (non-pectus related) comorbidities. It therefore will be very difficult to draw any clinically relevant conclusions and define implications for clinical practise. Due to the absence of a (non-pectus) control group, it will be difficult to define relationships between pectus and other conditions.

Reply 10:

Regarding the focus on all comorbidities, please see the reply to the related comment 2. Furthermore, please see the reply to comment 4 regarding the lack of a control group. Regarding clinical implications, please see changes for comment 18.

Changes in the text:

None.

Comment 11:

The title and running head do not concise. The title talks about any comorbidities present in patients with pectus excavatum, while the running title talks about comorbidities that are associated with pectus excavatum. For example, prior limb amputation may be a comorbidity present in a pectus excavatum patient but is not associated with the condition.

Reply 11:

We thank the review for pointing out this ambiguity and have changed the running title.

Changes in the text:

L. 4: “RUNNING TITLE: Comorbidities in Surgical Patients with Pectus Excavatum”

Comment 12:

Please do not use abbreviations like PE, but use pectus excavatum for readability purposes.

Reply 12:

We agree with the reviewer and have addressed this issue in the manuscript.

Changes in the text:

The abbreviation PE has been removed and spelled out throughout the document.

Comment 13:

An exclusion criterium is missing medical records. Please state in the results section how many patients were excluded due to missing medical records.

Reply 13:

We apologize for this omission and have added this information to the manuscript.

Changes in the text:

Ll. 112-113: "Patients were identified and included if registered under the procedure code for correction of pectus excavatum (n=1,047). Exclusion criteria was missing medical records (n=1)."

Comment 14:

Differences between prevalence of comorbidities were assessed for differences across gender groups. What is the rationale to assess gender differences? One could also stratify patients by age? Given the rationale that older patients have more comorbidities, however, what are the clinical implications to be sought by comparing both groups?

Reply 14:

The rationale for comparing comorbidities and previous medical conditions across

gender were 1) pectus excavatum affects the genders unevenly (the male to female ratio in our study was 5:1), 2) likewise, many conditions have different prevalences across genders. Furthermore, the reason for not comparing across age categories was, as mentioned by the reviewer, the inherent bias of comparing cumulated incidences of specific conditions across age categories - ie. the incidences rise with greater age for the most prevalent conditions as asthma, allergies, psychiatric comorbidities, etc. It was within the aim of this study, that in the case of a (some) condition(s) having particularly high prevalence – eg. as some authors advocate screening surgical pectus excavatum populations for Marfan syndrome – that these could be apparent and afterwards be investigated in to more specifically. The findings in this study do not encourage such a quest as our population, as previously stated, seems to be similar to the background population.

Changes in the text:

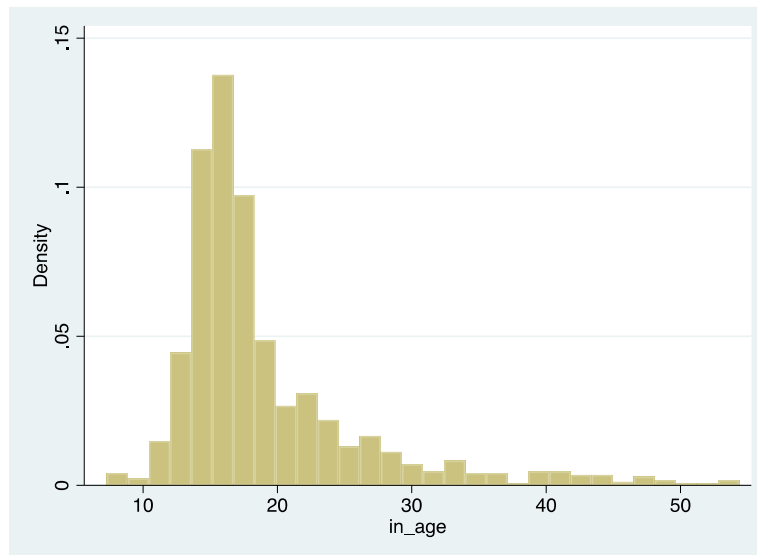
None.

Comment 15:

Please check whether the age of participants shows a non-normal distribution. With the high number of patients included, a normal distribution and thus the use of mean and SD is more likely.

Reply 15:

As shown in the histogram below, the age distribution was right skewed. Therefore, we presented data with non-normal distribution statistics.



Changes in the text:

None.

Comment 16:

1046 patients underwent surgical repair. What were the indications for repair?

Reply 16:

The indication for surgical repair was moderate to severe pectus excavatum (ll. 110-112). Please see the reply addressed to comment 1 for further explanation.

Changes in the text:

None.

Comment 17:

Line 112: 'treated'

Reply 17:

We apologize for the misspelling and this has been corrected.

Changes in the text:

Ll. 172-175: “Some of these patients had a history of scoliosis (9 patients), morbus Scheuerman (6 patients), Marfan syndrome (4 patients), muscular dystrophias (3 patients), Ehlers Danlohs syndrome (2 patients), and medically treated acne vulgaris (10 patients).”

Comment 18:

Please comment on the clinical consequences of the current study in the discussion section. Based on the presented results we can state that several comorbidities are present in pectus excavatum patients, however, nothing about their clinical consequence/implications and/or association to pectus excavatum? The added value of the study seems missing. For example. Hernias were observed predominantly in males while females had a higher prevalence of psychiatric comorbidity. Should we screen females for psychiatric comorbidities?

Reply 18:

Some authors suggest screening patients with pectus excavatum cardiac anomalies or connective tissue syndromes as Marfan syndrome (Behr. et al., 2019 (5) – a study with similar methodology but very different results and conclusions). The clinical implications of the findings in this paper suggest that a systematic screening of patients in our cohort would be ineffective and ultimately futile. This has been added to the text, although with precaution for this study’s limitations.

Changes in the text:

Ll. 59-61: “It seems that this patient category is comparable to the background population in this regard and our findings do not support screening this patient category for associated conditions.”

Ll. 235-236: “Thus, our findings do not support screening this patient category for associated conditions.”